2/18/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D1373B

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

JUN 5 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ms. Arlene Vidor
Baxter Healthcare Corporation
550 North Brand Boulevard
Glendale, CA 91203

An inspection of Baxter S.A., located at Boulevard Rene Branquart 80, 7860 Lessines, Belgium, was conducted from March 3 through 7, 1997. During the inspection, violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Part 211 were documented as follows:

1. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components and in-process materials conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] in that:

   a. data are not available to support the established operating parameters for lyophilizers used for final freeze drying of the Gammagard® and Polygam® products.

(b)(4) b. effectiveness of the [redacted] oven to achieve a 3 log reduction of a known endotoxin challenge has not been determined since 1988.

   c. data are not available to demonstrate adequate heat distribution within the [redacted] oven or the effectiveness of the established load pattern.

(b)(4) d. effectiveness of shipping procedures for biological indicators [redacted] has not been established. Records are not available to assure that biological indicators are maintained at the recommended storage temperature during shipment from the Round Lake facility to the Lessines facility

(b)(4)

e. effectiveness of shipping procedures for the non-sterile frozen Fraction II paste from the [redacted] facility has not been established.

2. Failure to establish and/or follow adequate written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100] in that:

a. there is no written procedure describing the process used to determine appropriate operating parameters of lyophilizers used for final freeze drying of the Gammagard® and Polygam® products.

(b)(4)

b. there is no written procedure describing endotoxin challenges for the [redacted] oven used for depyrogenation of finished product containers and media fill vials.

c. written procedures do not define specific test sites for smoke studies performed following integrity testing of HEPA filters.

3. Failure to establish an adequate system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)] in that data are not available to demonstrate that HEPA filtered air maintains a sufficient degree of laminarity during aseptic filling operations.

4. Failure to establish and/or follow appropriate written procedures designed to prevent microbial contamination of drug products purported to be sterile [21 CFR 211.113(b)] in that written procedures do not define specific sampling locations for monitoring microbial quality of air in the Class 100 areas.

5. Failure to maintain the following records [21 CFR 211.180]:

a. identity of individuals performing all required steps during aseptic media filling operations.

b. number of media fill vials discarded during aseptic media filling operations and the reason for discard.

c. identity of individuals performing required steps during integrity testing of HEPA filters.

6. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42(c)(10)(v)] in that solutions used for cleaning the aseptic processing areas are not sterilized prior to use.

During the inspection, the viral inactivation process for the Gammagard® and Polygam® products was described to our investigators as involving solvent/detergent treatment of a filtered suspension of Fraction II paste and subsequent incubation of the solution at ambient temperatures for at least one hour. Your product license specifies that solvent/detergent treatment is conducted at temperatures of [redacted]. Please provide clarification of the process and submit procedures pertaining to temperature monitoring during solvent/detergent treatment since approval of the process, approximately 1994 through the present.

The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as Responsible Head to assure that your establishment is in compliance with all requirements of the federal regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your March 21, 1997, written response which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Our evaluation of your March 21 response follows and is numbered to correspond to the sections/items listed on the Form FDA 483.

Validation and Production

FDA 483 item #2.a

Please submit a copy of your revised standard operating procedure (SOP) describing the bacterial endotoxin challenge for the [redacted] oven.

(b)(4)

FDA 483 item 2.b

A copy of the temperature distribution studies for the dry heat oven should be submitted upon completion.

FDA 483 item #3.a and b

A copy of revised SOP #QC-03-079 should be submitted.

FDA 483 item #7

Please submit a copy of the referenced validation studies supporting the effectiveness of shipping procedures for the Fraction II paste.

Air Handling Operations
FDA 483 item #1.a
Please submit a copy of the revised SOP defining specific test sites for smoke studies performed in the aseptic processing areas.

FDA 483 item #1.c
Upon completion, please submit a copy of your smoke studies demonstrating that HEPA filtered air maintains a sufficient degree of laminarity at the work surface during aseptic filling operations.

Environmental Monitoring
FDA 483 item #2
Please provide a copy of the revised SOP defining specific microbial sampling locations for environmental monitoring in the Class [redacted] areas. (b)(4)

FDA 483 item #3
A microbial challenge of the media with common microbial contaminants recovered from the manufacturing environment would provide a greater and more realistic challenge of the microbial growth media used for environmental monitoring. These microorganisms (normal microbial flora) would be less robust than the ATCC control standards currently in use.

You should notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. All corrective actions will be verified during reinspection of your facility.

Your reply should be sent to my attention in the Office of Compliance, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, HFM-600, Rockville, Maryland 20852-1448,

Sincerely,

Michael Dubzinski

for James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research

cc: Mr. Jean-Claude Andrieu
Director of Manufacturing Operations/Plant Manager
Baxter S.A.
Boulevard Rene Branquart 80
7860 Lessines, Belgium